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Mini-Review Article

Role of COVID-19 Genotype in Pathogenesis

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Abstract

Background: Coronaviruses are not new to us, and there are 15 different variants known to us. In the last 20 years, this is the fourth coronavirus outbreak, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be the deadliest among all, with the ability to continue producing more contagious variants. In this mini-review, we highlighted the genotypic variance of the pathogenesis of COVID-19.

Methodology: The article tracks the history and the genotypic variance of coronavirus. The literature was searched using the terms COVID-19, SARS-CoV-2, Coronavirus, genotypic variance etc., via Google Scholar and PubMed.

Results: Comparative modelling and molecular studies revealed some essential variations in the intermolecular interaction between Angiotensin-converting enzyme 2 (ACE-2) alleles and SARS-CoV-2 spike protein. A striking result is observed for two alleles, rs73635825 (S19P) and rs143936283 (E329G), of ACE-2. The low affinity to bind and absence of crucial residues during complex formation with SARS-CoV-2 spike protein of these alleles might be the reason behind intrinsic resistance against SARS-CoV-2 infection.

Conclusion: The SARS-CoV-2 Spike protein appears to be a promising immunogen for protection, but its role in preventing transmission remains unclear.

Keywords

COVID-19, Pandemic, Coronavirus, Severe Acute Respiratory Syndrome, AEC-2.

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Introduction

The emergence of Coronaviruses has occurred twice in the 21st century and causes worldwide epidemics and pandemics. These viruses were overlooked until the outbursts of SARS (severe acute respiratory syndrome) and MERS (Middle East Respiratory Syndrome), which then initiated vaccine research studies. A third outbreak detected in December 2019 from China has been identified as another variant of coronavirus, named COVID-19 by the World Health Organization (WHO)[1-3]. Moreover, the virus has created a noteworthy social and economic impact globally[4]. Several researches suggest that certain mutations may alter the pathogenesis, virulence, and/or transmission of RNA viruses[5]. Possibly, this process remains poorly studied among emergent coronaviruses in animals and humans. Understanding this challenging relationship between zoonotic diseases also needs to be evaluated for the economic influences of illness on domestic species such as cattle, along with the human health impacts[6]

SARS-CoV-2, which was recently identified as the cause of the Coronavirus Illness Pandemic of 2019 (COVID-19), has been classified as a zoonotic disease[7,8]. The emergence of SARS-CoV-1 in 2002 was also classified as a zoonotic disease, despite more than 500 betas (β) coronaviruses variants identified from bats in the state of an outbreak surrounding area, no particular host yet have been confirmed[8,9]. With the diversity that bats share among their species, population size, their wide distribution in various regions of the world and their migration rate, it can be assumed that bats are the forebear of this pathogen. A variety of this novel virus and its variants have been identified in humans and many animal and fowl species. HCoV-nl63 and HCoV-HKU1 from human avian infectious bronchitis virus (IBV) like coronaviruses in birds suggest the wide spectrum of the virus in living beings[9,10].

The occurrence of emerging infectious diseases (EIDs) has continuously been attributed to human influences on the environment, primarily through our food system (mostly cattle), implying that EIDs are avoidable [10,11]. As a result, COVID-19 has been proposed for inclusion as an "emerging infectious disease of suspected animal origin"[11].

Further, several aspects of human conduct and environmental factors were held responsible for the outbreak of 30 and more infective diseases, including various pathogens from rotavirus to MERS[12]. In addition, the environment has been altered as a result of the growing human population, people's migration across varied borders, the rapid development of air traffic, and changes in the atmosphere, allowing these novel infections to spread readily over the world.

History

Viruses causing respiratory infections have been the principal source of sickness and deaths in humans and animals worldwide since the 1930s. Around 200 immunoactive variants of influenza virus, rhinovirus, adenovirus, coronavirus, metapneumoviruses, orthopnuemoviruses have been identified as the culprit behind many respiratory tract infections or illness predominantly in humans[13,14]. Coronaviridea was said to be one of the deadly viruses causing respiratory sickness and discomfort[14]. It belongs to a positive-sense RNA family that has an outer protective viral coat. When this pathogen is closely examined under an electron microscope, it is revealed that a novel corona is present around it. *Coronaviridae* is a family of viruses with a positive-sense RNA that possesses an outer viral coat. Also reported that to have a unique corona around when studied under an electron microscope. For most respiratory disorders in humans, this viral family is the primary cause of it[15]. Although, as mentioned, this virus has gained limited interest from researchers until the year 2003, the outbreak of SARS in 2003 and MERS in 2012 seems to be the first epidemic of the 21st century[11,12]. Because of their enormous genetic diversification, frequent recombination of their genome, and elevated activity at human-animal alliance represents an ongoing threat to human health[16].

It is reported by scientists that because there is a difference in one amino acid at the receptor-binding region of S-protein in Pangolin Coronavirus in comparison with SARS-CoV-2, it gives rise to a possibility that Pangolin-Cov might be an intermediary host[17-18]. Researches also suggest that there is a 96% similarity in the genes array of SARS-Cov-2 and coronavirus of bats that is RatG[13]. Reportedly, SARS-CoV-2 has shown poor growth and replication rate in dogs, pigs, ducks and chickens but grows efficiently in cats and ferrets[19].

Coronaviruses have been assigned to four sub-domains according to their characteristics. These sub-domains are alpha, beta, gamma and delta. Among these beta, sub-groups are human pathogens[20,21]. Many studies support that HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), MERS-CoV (the Middle East Respiratory Syndrome Coronavirus), and the recent SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2 known as COVID-19) are included in the Betacoronavirus which are human pathogens causing respiratory diseases in humans. The members of this genus of the coronavirus family have the tendency to extend their pathogenesis and their adaptations according to human host[21,22].

Structure

When studied under an electron microscope, it appears to have a characteristic solar corona (a crown-like) named Coronaviruses. There are two distinctive envelope proteins observed during the examination. First one is the Spike glycoproteins, which are mainly responsible for receptor binding and cell fusion[23], and the other one is a transmembrane glycoprotein (M), primarily involved in asexual budding and envelop development and also plays an essential role in virion assembly[24]. Another additional glycoprotein, the haemagglutinin-esterase (HE), is witnessed in some viruses. An association is found between the viral genome and a basic phosphoprotein (N) in the capsid. It is a long non-segmented, positive single-stranded RNA with a length of 26-32 kb. This makes it the longest RNA viral genome identified yet. It contains around 7 to 10 diverse open reading frames. The RNA molecule is secured with a methylated cap in 5' and a poly-A tail in 3'[23,24]. Adherence with the host cell and penetration capacity play a crucial role in the pathogenesis. It is attained by the interaction between glycoprotein S and ACE-2, which is a surface carboxypeptidase which randomly scattered in human tissues[25]. Genetic factors, age, gender has an impact on the binding affinity of the S-glycoprotein with ACE-2. This can justify the low case fatality rate (CFR) in infants and children as compared to those who are 80 years or above as the data suggest that there is 0% CFR in patients under eight years of age vs. 22% for patients 80 above[26]. Further, the ACE-2 expression increases in the presence of comorbid disorders like obesity, pre-existing chronic cardiopulmonary disease, cancer, and use of immunosuppressive drugs, make the patients more vulnerable to develop serious infections[26].

Genotype and Phenotype

The novel virus's morbidity and mortality were studied to be mediated by functional loss of ACE-2[27,28]. The homolog of ACE-2 affects through cleavage product angiotensin derived from angiotensin II, which induces inflammation, oxidation and vasoconstriction through the metabolism of bradykinin and dopamine-serotonin pathway. Pneumocytes especially those, which have the highest expression of ACE-2, including type 2 pneumocytes, alveolar parenchyma, appear to be the primary host. However, the defender cells such as alveolar macrophages and pulmonary dendritic cells may also serve as a host to the least extent. The membranes lining the nasal cavities, renal tubular cells, vascular, digestive and respiratory tract endothelium could be the alternative targets of the pathogen[29].

As stated, there is a significant role of the surface S protein of the virus that is causing the infection. It belongs to trimeric class 1 T.M., the glycoprotein which plays a crucial part in letting the virus enter the host cell. This glycoprotein is represented by all kinds of HCoVs, HIV glycoprotein 160, Env), influenza virus (influenza hemagglutinin, H.A.), paramyxovirus (paramyxovirus F), and Ebola (Ebola

virus glycoprotein) [30]. During viral infection, it aids receptor identification, cell attachment, and fusion[31, 32]. The basic receptor binding unit of S protein is a trimer that is attached to the surface of the viral envelope[31,33]. This trimer is subdivided into S1 and S2 domains. S1 has the receptor-binding domain (RBD), which is primarily involved in the attachment of the virus with the receptor. On the contrary, heptapeptide repeat sequence (including HR1, HR2), rich S2 domain is important for the fusion of the virus[33]. The subunits have distinct subregions that recognize specific receptors depends on viral species[32].

Some comparative modelling and molecular studies suggested certain essential alterations in the interlink between ACE-2 alleles and SARS-CoV-2 spike protein. A striking result is observed for two alleles**,** rs73635825 (S19P) and rs143936283 (E329G), of ACE-2. The low affinity to bind and absence of crucial residues during complex formation with SARS-CoV-2 spike protein of these alleles might be the reason behind intrinsic resistance against SARS-CoV-2 infection. Hence, it is quite a possibility that in the next gene selection, these alleles may go through positive selection for SARS-CoV-2. Though, as the protein-ligand and protein to protein interaction are vastly dynamic thus the implementation of molecular dynamics modulation could assist in confirming the lack of certain residues, which causes hindrance in the fusion of SARS-CoV-2 spike protein and the alleles of ACE-2. Along with this, empirical methods for determining the capacity to make intermolecular bonds in the complexes could potentially be useful in this area[34].

The current study focuses on ACE-2 potential alleles that may influence COVID-19 susceptibility and resilience. It also serves as a model for future research on the recently discovered molecule TMPRSS2, which is needed for priming the spike protein for virus access into the cell[35]. Lastly, age groups, nationalities and race may have a huge impact on the recovery rate and clinical signs and symptoms of COVID-19[36]. The occurrence of ACE-2 variations such rs73635825 (S19P) and rs143936283 (E329G) could explain some, if not all, of the COVID-19's favourable prognosis[34,36].

In terms of immune responses, there are structural modifications made in the host cell by replication of the virus in the pneumocytes and other endothelial cells that stimulate the innate and adaptive immune system, which leads to the progression of disease[21,26,37]. The innate immune cells stimulate the lymphocytes, T lymphocytes, macrophages, dendritic cells, and antibody production Immunoglobulin (Ig) M isotype and IgG isotype. The viral particles coated with the antibodies were identified by macrophages and disseminated by phagocytes[37]. Also, there is the induction of endothelial cytokines and increased capillary permeability, which leads to platelet activation hypercoagulability, hypo fibrinolysis, and complement overactivation, playing a role in thrombus formation mediated by the immune response within the lung parenchyma–pulmonary phase. In addition, proteins expressed by SARS-CoV-2 can inhibit the formation of interferon. Studies revealed that in patients who are older, disrupted immunity, with other comorbidities, and high viral count, T-cell lymphopenia can be evaluated as an indicator for the severity of the infection[26,37]. In addition, viral sepsis, which is defined as fatal organ dysfunction induced by an altered host response to pathogens, may play a role in multiple organ failure.

The global epidemiological figures stated the prevention is the best way to fight against COVID-19[35,38]. However, untiring efforts in finding effective interventions are needed until potent vaccines or cures are available. Maintaining a safe distance, keeping good personal hygiene, closure of educational, industrial, and public places, regulatory actions taken by the governmental authorities regarding the lockdowns and limitations on public gatherings along with ceased internal borders are the necessary precautions to control the spread of the infection[39]. There is diversity in these precautionary measures across the globe according to economic, social, geographical and political aspects.

Conclusion

The SARS-CoV-2 Spike protein emerged as a potential immunogen for defence against the pathogen, but its role in preventing transmission is still unclear. Other approaches to prevention may be including monoclonal antibodies, hyperimmune globulin, and convalescent titer.

Conflicts of Interest

The authors have declared that no competing interests exist.

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